

DRUG METABOLISM AND DISPOSITION

A Publication of the American Society for Pharmacology and Experimental Therapeutics

July 2007

Vol. 35, No. 7

CONTENTS

PERSPECTIVE

CYP1A Induction and Human Risk Assessment: An Evolving Tale of *in Vitro* and *in Vivo* Studies. *Qiang Ma and Anthony Y. H. Lu*

1009

Wei-Cheng Chen, Shih-Jung Lan, Chiung-Tong Chen, Yu-Sheng Chao, Ling Chang, Hsu-Yi Sun, and Teng-Kuang Yeh

1042

SHORT COMMUNICATION

The Phosphoinositide-Specific Phospholipase C Inhibitor U73122 (1-(6-((17 β -3-Methoxyestra-1,3,5(10)-trien-17-yl)amino)hexyl)-1H-pyrrole-2,5-dione) Spontaneously Forms Conjugates with Common Components of Cell Culture Medium. *Nicola E. Wilsher, Will J. Court, Ruth Ruddle, Yvette M. Newbatt, Wynne Aherne, Peter W. Sheldrake, Neil P. Jones, Matilda Katan, Suzanne A. Eccles, and Florence I. Raynaud*

1017

□ Possible Bioactivation Pathways of Lamotrigine. *Wei Lu and Jack P. Uetrecht*

1050

□ Effect of Perinatal Low Protein Diets on the Ontogeny of Select Hepatic Cytochrome P450 Enzymes and Cytochrome P450 Reductase in the Rat. *Ganesh Cherala, Bernard H. Shapiro, and Anil P. D'mello*

1057

Effect of Arylamine Acetyltransferase *Nat3* Gene Knockout on *N*-Acetylation in the Mouse. *K. S. Sugamori, D. Brenneman, S. Wong, A. Gaedigk, V. Yu, H. Abramovici, R. Rozmahel, and D. M. Grant*

1064

ARTICLES

Esterase Inhibition Attribute of Grapefruit Juice Leading to a New Drug Interaction. *Ping Li, Patrick S. Callery, Liang-Shang Gan, and Suresh K. Balani*

1023

Metabolism, Pharmacokinetics, and Excretion of a Nonpeptidic Substance P Receptor Antagonist, Ezlopitant, in Normal Healthy Male Volunteers: Characterization of Polar Metabolites by Chemical Derivatization with Dansyl Chloride. *Chandra Prakash, John O'Donnell, and S. Cyrus Khojasteh-Bakht*

1071

Valproic Acid Induces CYP3A4 and MDR1 Gene Expression by Activation of Constitutive Androstane Receptor and Pregnane X Receptor Pathways. *Lukas Cervený, Lucie Svecova, Eva Anzenbacherova, Radim Vrzal, Frantisek Staud, Zdenek Dvorak, Jitka Ulrichova, Pavel Anzenbacher, and Petr Pavek*

1032

Identification of a Novel Glutathione Conjugate of Flutamide in Incubations with Human Liver Microsomes. *Ping Kang, Deepak Dalvie, Evan Smith, Sue Zhou, and Alan Deese*

1081

Biotransformation of 6-Methoxy-3-(3',4',5'-trimethoxy-benzoyl)-1H-indole (BPR0L075), a Novel Antimicrotubule Agent, by Mouse, Rat, Dog, and Human Liver Microsomes. *Hsien-Tsung Yao, Yu-Shan Wu, Yi-Wei Chang, Hsing-Pang Hsieh,*

Intestinal First-Pass Metabolism via Carboxylesterase in Rat Jejunum and Ileum. *Kenji Masaki, Mitsuru Hashimoto, and Teruko Imai*

1089

Continued on next page

Drug Metabolism and Disposition (ISSN 0090-9556) is published monthly (one volume per year) by the American Society for Pharmacology and Experimental Therapeutics, 9650 Rockville Pike, Bethesda, MD 20814-3995; e-mail: info@aspet.org; Web site: http://www.aspet.org Periodicals postage paid at Bethesda, MD and at additional mailing offices. POSTMASTER: Send address changes to *Drug Metabolism and Disposition*, 9650 Rockville Pike, Bethesda, MD 20814-3995. Subscription Rates: U.S.: \$353.00 for institutions and \$184.00 for non-ASPET members. Outside the U.S.: \$423.00 for institutions and \$254.00 for non-ASPET members. Single copy: \$35.00. GST Tax Number for Canadian subscribers: BN:13489 2330 RT. Indexed or abstracted by *Biochemistry & Biophysics Citation Index*®, *Biological Abstracts*, *BIOSIS Previews Database*, *BioSciences Information Service*, *Current Awareness in Biological Sciences*, *Current Contents*®/Life Sciences, *EMBASE/Excerpta Medica*, *Index Medicus*, *International Pharmaceutical Abstracts*, *Medical Documentation Service*®, *Reference Update*®, *Research Alert*®, *Science Citation Index*®, *SciSearch*®, and *SIIC Data Bases*. Copyright © 2007 by the American Society for Pharmacology and Experimental Therapeutics. All rights reserved. Printed in the U.S.A.

The Disposition of Prasugrel, a Novel Thienopyridine, in Humans. <i>Nagy A. Farid, Richard L. Smith, Todd A. Gillespie, T. James Rash, Patrick E. Blair, Atsushi Kurihara, and Mark J. Goldberg</i>	1096
Selective Tissue Distribution of Tibolone Metabolites in Mature Ovariectomized Female Cynomolgus Monkeys after Multiple Doses of Tibolone. <i>H. A. M. Verheul, M. L. P. S. van Iersel, L. P. C. Delbressine, and H. J. Kloosterboer</i>	1105
Pharmacokinetic Parameters of Tibolone and Metabolites in Plasma, Urine, Feces, and Bile from Ovariectomized Cynomolgus Monkeys after a Single Dose or Multiple Doses of Tibolone. <i>H. A. M. Verheul, C. J. Timmer, M. L. P. S. van Iersel, L. P. C. Delbressine, and H. J. Kloosterboer</i>	1112
Application of the Dispersion Model to Describe Disposition Kinetics of Markers in the Dual Perfused Rat Liver. <i>Selma Sahin and Malcolm Rowland</i>	1119
Cytochrome P450 Eicosanoids are Activators of Peroxisome Proliferator-Activated Receptor α . <i>Valerie Y. Ng, Yong Huang, L. Manmohan Reddy, John R. Falck, Emil T. Lin, and Deanna L. Kroetz</i>	1126
Timolol Metabolism in Human Liver Microsomes Is Mediated Principally by CYP2D6. <i>Marjo Volontinen, Miia Turpeinen, Ari Tolonen, Jouko Uusitalo, Jukka Mäenpää, and Olavi Pelkonen</i>	1135
Improvement of the Oral Drug Absorption of Topotecan through the Inhibition of Intestinal Xenobiotic Efflux Transporter, Breast Cancer Resistance Protein, by Excipients. <i>Tetsuo Yamagata, Hiroyuki Kusuhara, Mariko Morishita, Kozo Takayama, Hassan Benameur, and Yuichi Sugiyama</i>	1142
The Prokinetic Cinitapride Has No Clinically Relevant Pharmacokinetic Interaction and Effect on QT during Coadministration with Ketoconazole. <i>Marta Robert, Miquel Salvà, Rosa Segarra, Marco Pavesi, Ramón Esbri, David Roberts, and Georg Golor</i>	1149
In Vitro Metabolic Characterization, Phenotyping, and Kinetic Studies of 9cUAB30, a Retinoid X Receptor-Specific Retinoid. <i>Gregory S. Gorman, Lori Coward, Corenna Kerstner-Wood, Lea Cork, Izet M. Kapetanovic, Wayne J. Brouillette, and Donald D. Muccio</i>	1157
Abcg2/Bcrp1 Mediates the Polarized Transport of Antiretroviral Nucleosides Abacavir and Zidovudine. <i>Guoyu Pan, Nagdeep Giri, and William F. Elmquist</i>	1165
CYP2C9 Protein Interactions with Cytochrome b_5 : Effects on the Coupling of Catalysis. <i>Charles W. Locuson, Larry C. Wienkers, Jeffrey P. Jones, and Timothy S. Tracy</i>	1174
Predominant Contribution of UDP-Glucuronosyltransferase 2B7 in the Glucuronidation of Racemic Flurbiprofen in the Human Liver. <i>Yuji Mano, Takashi Usui, and Hidetaka Kamimura</i>	1182
Metabolism and Disposition of a Selective α_7 Nicotinic Acetylcholine Receptor Agonist in Humans. <i>Christopher L. Shaffer, Mithat Gunduz, Renato J. Scialis, and Annie F. Fang</i>	1188
Absorption, Metabolism, and Excretion of [14 C]MK-0524, a Prostaglandin D ₂ Receptor Antagonist, in Humans. <i>Bindhu Karanam, Maria Madeira, Scott Bradley, Larissa Wenning, Rajesh Desai, Eric Soli, David Schenk, Allen Jones, Brian Dean, George Doss, Graigory Garrett, Tami Crumley, Ajay Nirula, and Eseng Lai</i>	1196
Esterase Inhibition by Grapefruit Juice Flavonoids Leading to a New Drug Interaction. <i>Ping Li, Patrick S. Callery, Liang-Shang Gan, and Suresh K. Balani</i>	1203
Impact of Genetic Knockout of PEPT2 on Cefadroxil Pharmacokinetics, Renal Tubular Reabsorption, and Brain Penetration in Mice. <i>Hong Shen, Scott M. Ocheltree, Yongjun Hu, Richard F. Keep, and David E. Smith</i>	1209
Selective Toxicity of Aristolochic Acids I and II. <i>Shinya Shibutani, Huan Dong, Naomi Suzuki, Shiro Ueda, Frederick Miller, and Arthur P. Grollman</i>	1217
Role of CYP3A and CYP2E1 in Alcohol-Mediated Increases in Acetaminophen Hepatotoxicity: Comparison of Wild-Type and <i>Cyp2e1</i> (-/-) Mice. <i>Kristina K. Wolf, Sheryl G. Wood, Jenna L. Allard, Jane A. Hunt, Nadia Gorman, Brooke W. Walton-Strong, Juliana G. Szakacs, Su X. Duan, Qin Hao, Michael H. Court, Lisa L. von Moltke, David J. Greenblatt, Vsevolod Kostрубsky, Elizabeth H. Jeffery, Steven A. Wrighton, Frank J. Gonzalez, Peter R. Sinclair, and Jacqueline F. Sinclair</i>	1223

Contents (cont'd.)


Risk Assessment for Drug-Drug Interaction Caused by Metabolism-Based Inhibition of CYP3A Using Automated in Vitro Assay Systems and Its Application in the Early Drug Discovery Process. *Akiko Watanabe, Koichi Nakamura, Noriko Okudaira, Osamu Okazaki, and Ken-ichi Sudo* **1232**

Isolation and Characterization of Polyspecific Mouse Organic Solute Carrier Protein 1 (mOscp1). *Yasuna Kobayashi, Ayumi Tsu-*

chiya, Tomofumi Hayashi, Noriko Kohyama, Masayuki Ohbayashi, and Toshinori Yamamoto **1239**

ERRATUM

Correction to “Three-Dimensional Quantitative Structure-Activity Relationship Analysis of Human CYP51 Inhibitors”. *S. Ekins, D. C. Mankowski, D. J. Hoover, M. P. Lawton, J. L. Treadway, and H. J. Harwood, Jr.* **1246**

 Supplemental material is available online at <http://dmd.aspetjournals.org>.

About the cover: A diagram showing the relationship between % remaining and the therapeutic blood or plasma concentration of 171 marketed compounds in which in vivo DDI information was incorporated. See the article by Watanabe et al. in this issue on page 1232.